REMARKS

Reconsideration of this application is requested in view of the amendments to the claims and the remarks presented herein.

The claims in the application are claims 1, 3, and 5 to 18, all other claims having been cancelled.

Responsive to the Examiner's requirement for a substitute specification, the same is submitted herewith and the specification contains no new matter. Therefore, a marked up copy is not being submitted since it is a copy of the original application.

Claims 1 to 18 were rejected under 35 USC 112, second paragraph, as being indefinite. The Examiner objected to the expression "suitable excipients" in line 10 of claim 1 and objected to the use of improper Markush terminology. Claim 8 was objected to as containing a trade name.

Applicants respectfully traverse this ground of rejection since the amended claims are believed to properly define the invention. The expression "suitable excipients" no longer appears in claim 1 and proper Markush terminology has been used. In addition, the trade name has been replaced with the description set forth on page 5 of the application. Therefore, the amended claims properly define the invention and withdrawal of these grounds of

rejection is requested.

All of the claims were rejected under 35 USC 103 as being obvious over the Saunal et al reference which corresponds to U.S. Patent No. 6,010,716 and the Winters et al '409 reference taken in view of the Eibl et al patent, the Merck Index and Remmington's Pharmaceutical Sciences. The Examiner states that the Saunal et al reference teaches a transdermal topical formulation of nomegestrol using a solvent, an absorption promoting agent, an active and a film-forming agent. The Winters et al reference describes a topical formulation of 19-nor progesterone for systemic delivery of an active. The Examiner states that the primary references do not teach the use of propylenglycol, isopropylidene glycerol, isopropylideneglycerol, anionic copolymer of methacrylic acid and ethyl acetate and carbomer as carrier materials nor the use of gelling agents. The Eibl et al patent is cited to show the use of propyleneglycol and copolymers of methylacrylic acid and ethyl acrylate as auxiliary agents in topical formulations. The Examiner states that the Merck Index teaches isopropylideneglycerol as a solubilizing agent the Remmington's Pharmaceutical Sciences teaches that the carbomer is useful as a gelling and emulsifying agent and the Examiner deems that it would be obvious to formulation nomegestrol in a topical formulation of a gelling agent and other carrier materials.

Applicants respectfully traverse these grounds of rejection

since the combination of the prior art, which the Examiner has created with the benefit of Applicants' disclosure, would not teach Applicants' invention to one skilled in the art without Applicants' teaching. The present invention relates to a topical hormonal composition with a systemic effect for the correction of progesterone deficiency in premenopausal women and for hormone replacement in menopausal women containing as the active ingredient nomegestrol or its esters or ethers, a vehicle allowing the systemic passage of the active principal selected from the group consisting of a solubilizing agent, an absorption promoter, a film-forming agent or a gelling agent or mixtures thereof combined with a suitable excipient for the production of a gelled and/or film-forming pharmaceutical. Applicants' compositions are not for topical use but for systemic use. Intended use does not lend any patentable weight to composition claims.

The Saunal et al reference relates to a composition for the transdermal delivery comprising an active ingredient which could be nomegestrol acetate, optionally a polymeric release matrix capable of forming a flexible film when dried which matrix is selected from the group consisting of cellulose polymers or copolymers and vinyl-pyrrolidone, vinyl acetate copolymers and a physiologically non-aqueous solvent capable of dissolving the release matrix and the transcutaneous absorption promoter quickly removing same by evaporation from the skin.

There is a major difference between a transdermal composition

and a gel with systemic activity. A transdermal composition is made of a small reservoir affixed on a strip of plastic material and the reservoir is faced to the skin. The reservoir usually contains a large amount of an active ingredient dissolved in a lipophilic diluent and the active ingredient diffuses from the lipophilic phase to the skin whereby it passes through the skin. The objective of such a preparation is to ensure a delayed or protracted duration of the diffusion of the active ingredient through the skin. The transdermal device is not intended to have the product reach the bloodstream but is merely intended to diffuse the active ingredient from the reservoir through the skin and the compounds present in the reservoir are selected due to their high lipophilicity and are compounds such as estradiol, scopolamine, nicotine and the like to be sure they will pass the skin barrier.

But Applicants' formulation has absolutely nothing to do with this since the purpose of the invention is to ensure optimum passage of the active and principle, nomegestrol, through the skin and into the bloodstream. Therefore, the Saunal et al reference in no way relates to Applicants' invention. The purpose of the present invention is to ensure optimum passage of the active principal nomegestrol through the skin.

Synthetic progesterones have the main drawback of showing very poor diffusion properties through the skin due to their lipophilic character. The compositions of Applicants' invention need a

precise balance between solubility of the active principal in the vehicle and its ability to diffuse through the skin towards the bloodstream. That is why the mixture proportion of the preferred solubilizing agents suitable for this composition is the main point of Applicants' invention. The effectiveness of the pharmaceutical composition is the result of the proper combination and term of dosage of all of the excipients.

In Applicants' invention, the preferred solubilizing agent is a ternary mixture or a quaternary mixture of 95% ethanol/water/propyleneglycol and optionally Labrasol and in which the percentage of 95% ethanol varies from 30 to 50%, the water from 30 to 60% and the proplyeneglycol from 2 to 20% and the Labrasol from 3 to 7%. These are the main constituents for permitting nomegestrol to pass through the cutaneous barrier. The Saunal et al compositions do not contain propyleneglycol which contributes to the effectiveness of the diffusion through the skin of Applicants' compositions. Saunal et al did not test any examples of compositions containing 19-nor progesterone derivatives and not specifically nomegestrol acetate but only reported similar compositions containing estradiol which are more easily obtained and satisfactorily efficient due to the high lipophilicity of estradiol and its derivatives. Saunal et al only postulates the possibility that these compositions contain nomegestrol acetate and nothing teaches the effectiveness of Applicants' pharmaceutical compositions since it is known to be difficult to obtain good

clinical results when the excipient mixture proportions are not well balanced. Nomegestrol acetate is known not to be as highly lipophilic as estradiol although, the compound has a balance in favor of lipophilicity but the tendency to hydrophilicity is considerable. There is no way to obtain Applicants' gel having systemic activity with the active ingredients being highly lipophilic.

With respect to the secondary references cited by the Examiner, Applicants will concede that they teach the use of all the pharmaceutical excipients known but the aim of the present invention is not to use a composition with known ingredients but to provide a specific pharmaceutical composition combining precise components for the beneficial use of systemic delivery of the nomegestrol and/or its esters and ethers. Therefore, the combination of the prior art, which the Examiner has made with the benefit of Applicants' disclosure, would not lead one skilled in the art to Applicants' invention and withdrawal of this ground of rejection is requested.

In view of the amendments to the claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
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Enclosures

1. A gelled and/or film-forming topical hormonal composition with systemic effect for treating progesterone deficiency in pre-menopausal women and for hormone replacement in menopausal women comprising a) 0.05 to 1% by weight of the composition of at least one active principle selected from the group consisting of nomegestrol, and ethers and esters thereof, b) at least one vehicle permitting systemic passage of active principle selected from the group consisting of a solubilizing agent, an absorption promotor, a film-forming agent and a gelling agent and c) optionally an excipient.

CLAIMS

A gelled and/or film-forming

1. Topical hormonal composition with systemic effect for ~~the correction of~~ treating progesterone deficiency in premenopausal women and for hormone replacement in menopausal women, ~~characterized in that it includes~~ comprising a) 0,05 to 1% by weight of the composition of at least one ~~as~~ active principle, selected from the group consisting of nomegestrol and ethers esters thereof, b) at least one ~~a~~ vehicle permitting ~~the~~ systemic passage of ~~the said~~ active principle ~~chosen~~ from the group consisting ~~comprising~~ a solubilizing agent, an absorption promoter, a film-forming agent selected and a gelling agent ~~or their mixtures~~, and c) optionally one excipient ~~combined with or mixed with suitable excipients for the production of a gelled and/or film-forming pharmaceutical form.~~

2. Topical hormonal composition with systemic effect ~~according~~ to claim 1, characterized in that the progestogen ~~derived from~~ 19-nor progesterone is nomegestrol and/or one of its esters or ethers.

A

3. Topical hormonal composition with systemic effect ~~according to~~ of claim 1 ~~or claim 2,~~ wherein ~~characterized in that the progestogen derived from 19-nor progesterone is~~ nomegestrol acetate is used

4. Topical hormonal composition with systemic effect ~~according~~ to any one of the claims 1 to 3, characterized in that the ~~quantity~~ of nomegestrol or of one of its esters or ethers varies from 0.05 ~~to 1%~~ by weight of the total composition.

A

5. Topical hormonal composition with systemic effect ~~according to~~ of claim 1, wherein ~~characterized in that~~ the quantity of nomegestrol or of one of its esters or ethers is about 0.4 % by weight of the total composition.

A

6. Topical hormonal composition with systemic effect ~~according to any one~~ of ~~the~~ claims 1 ~~to 5,~~ containing at least one ~~characterized in that the~~ solubilizing agent ~~is chosen~~ selected from the group consisting ~~comprising~~ water, alcohols, propyleneglycol and a C_8/C_{10} polyoxyethylene glycosyl glyceride ~~or their mixtures~~.

A

7. Topical hormonal composition with systemic effect ~~according to any one~~ of ~~the~~ claims 1 ~~to 6,~~ wherein ~~characterized in that~~ the solubilizing agent is a ternary mixture of 95% ethanol / water /

propyleneglycol, in which the percentage of 95% ethanol ~~varies from~~ is 30 to 50 %, that of water ~~from~~ is 30 to 60 % and that of propyleneglycol ~~from~~ is 2 to 20 % .

8. A topical hormonal composition with systemic effect ~~according to any one~~ of ~~the~~ claims 1 ~~to 6,~~ ~~characterized in that the~~ containing a solubilizing agent of a quaternary mixture of 95% ethanol / water / ~~Labrasol®~~ caprylocaproyl polyoxyethylene glycol glyceride / propyleneglycol, in which the percentage of 95% ethanol ~~varies from~~ is 30 to 50 %, that of water ~~from~~ is 30 to 60 %, that of ~~Labrasol® from~~ the glyceride is 3 to 7 % and that of propyleneglycol ~~from~~ is 2 to 20 %.

9. A topical hormonal composition with systemic effect ~~according to any one~~ of ~~the~~ claims 1 ~~to 8,~~ ~~characterized in that the~~ containing an absorption promoter ~~is chosen~~ selected from the group consisting of isopropylideneglycerol, α-tocopheryl polyethyleneglycol 1000 succinate and monoethyl ether of diethylene glycol.

10. A topical hormonal composition with systemic effect ~~according to~~ of claim 9, ~~characterized in that~~ wherein the absorption promoter is isopropylideneglycerol.

11. A topical hormonal composition with systemic effect according to any one of ~~the~~ claims 1 ~~to~~ 10, ~~characterized in that the~~ containing a gelling agent ~~is chosen~~ selected from the group consisting of cellulose derivatives and acrylic derivatives.

12. A topical hormonal composition with systemic effect ~~according to~~ of claim 11, ~~characterized in that the cellulose derivative is~~ containing hydroxypropylmethylcellulose.

13. A topical hormonal composition with systemic effect ~~according to~~ of claim 11, ~~characterized in that the acrylic derivative is~~ containing a carbomer.

14. A topical hormonal composition with systemic effect ~~according to any one~~ of ~~the~~ claims 1 ~~to~~ 13, ~~characterized in that the~~ containing a film-forming agent ~~is chosen~~ selected from the group consisting of cellulose derivatives, methacrylic derivatives and polyvinylpyrrolidone derivatives.

15. A topical hormonal composition with systemic effect ~~according to~~ of claim 14, ~~characterized in that the cellulose derivative is~~ containing hydroxypropylmethylcellulose acetate succinate.

16. Topical hormonal composition with systemic effect ~~according to~~ of claim 14, ~~characterized in that the methacrylic derivative is~~ containing an aqueous dispersion of an anionic copolymer of methacrylic acid and ethyl acrylate as the film-forming agent

17. Topical hormonal composition ~~according to any one~~ of ~~the~~ claims 1 ~~to 16, characterized in that it is~~ in the form of a gel or a film-forming gel ~~and in that it contains, in~~ containing an aqueous-alcoholic mixture with 8 % of propyleneglycol and 3 % of isopropylidene glycerol.